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Commentary

# It's not just size that matters: Challenges in studying obesity and female-specific cancers

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In *The Lancet Regional Health – Western Pacific*, Yong Sang Song and colleagues evaluated the association of obesity with risks of breast, endometrial, ovarian, and cervical cancers, by menopausal status in over 2.7 million Korean women [1]. The investigators demonstrated a significant positive association between elevated body mass index (BMI) and waist circumference (WC), with risk of postmenopausal breast, and pre- and postmenopausal endometrial, ovarian, and cervical cancers, with the strongest associations observed for endometrial cancer. BMI and WC were associated with decreased risk of premenopausal breast cancer. The findings from Park et al. are largely consistent with data from the literature in Asian and Western populations [2–4] and highlight the importance of considering ethnic variation with respect to associations of obesity with cancer risk [4].

When interpreting the findings from Park et al., and other large epidemiologic studies evaluating obesity and cancer risk, there are several important factors to consider, including: 1) Exposure assessment; 2) tumor heterogeneity; and 3) underlying mechanisms. 1) *Exposure assessment.* BMI is a relatively cheap and easily ascertained surrogate marker of adiposity commonly used in epidemiologic studies based on self-report or direct measurement. However, BMI cannot distinguish between lean and adipose tissue mass, and lacks information about the distribution of body fat, e.g., subcutaneous, visceral, and ectopic fat components. Several studies have demonstrated that visceral adipose tissue, and more recently ectopic fat, are metabolically active and associated with increased risk of morbidity and mortality, whereas abdominal subcutaneous fat has shown much weaker associations [5]. WC has been used as a surrogate measure of abdominal fat which includes both subcutaneous and visceral fat components. Findings from Park et al. suggest that WC may provide independent risk information beyond BMI; however, other studies have shown limited evidence that WC is a better predictor of cancer risk than BMI alone, suggesting it is a poor marker for central adiposity [6]. While imaging techniques can be used to visualize and quantify different types of adipose tissue, they are expensive and not feasible for most epidemiologic studies. Thus, valid, simple, and more affordable approaches are needed [5]. Another challenge related to exposure assessment includes the timing of obesity exposure and cancer risk, which as demonstrated by Park et al., and others, may vary in relation to critical periods of susceptibility such as menopause and other hormonally related processes like menarche, and pregnancy. Accounting for these critical periods in epidemiologic studies is challenging and requires repeat measurements over a long period of time to avoid misclassification. Electronic health records with good ascertainment of BMI at various time points linked to clinical visit information may provide opportunities to address some of these challenges.

2) *Tumor Heterogeneity*. Associations between obesity and female-specific cancers are subtype specific. For example, the relationship between obesity and breast cancer risk varies by estrogen and progesterone receptor status [7], and the magnitude of the association between obesity and endometrial cancer is much stronger for "type 1" endometrioid compared to "type 2" non-endometroid (e.g., serous, clear cell) tumors [8]. The link between obesity and ovarian cancer is an example of how associations can be masked when distinct subtypes are grouped together, as large pooled analyses suggest positive relationships between obesity and the more rare endometrioid and mucinous subtypes, but not with the most common serous subtypes [9]. The study conducted by Park et al., did not include subtype information, therefore the contribution of subtype specific effects to the overall observed associations remains unclear and an important area for future research. Studies across multiple sites that are etiologically related on a subtype level (e.g., endometrioid ovarian and endometrial cancers), may reveal novel biological associations.

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3) *Underlying Mechanisms.* Obesity has long been recognized as a risk factor for female-specific cancers, but the mechanisms underlying these associations remain elusive. Proposed biological pathways include alterations in insulin signaling, sex hormone pathways, and inflammatory pathways involving adipokines, macrophages, and other immune cells, yet site and subtype-specific mechanisms are not well-characterized [6]. Furthermore, it is important to also consider non-biological mechanisms. For example, in approximately one million women undergoing cervical screening, obesity was associated with missed detection of cervical precancers resulting in an increased risk of cervical cancer, likely owing to greater difficulties in cervical sampling, visualization and treatment of precancers in obese patients [10]. These findings have important implications for clinical practice and epidemiologic research on obesity and cervical cancer risk and serve as illustrative example of the importance of considering both biological and non-biological mechanisms.

Obesity is a major global public health problem with significant implications for cancer risk; however, limited mechanistic evidence linking obesity and site-specific cancers has hindered progress towards understanding, preventing, and treating obesity-associated cancers. Large, population-based epidemiologic studies can provide important clues about potential associations, but these studies need to be coupled with in-depth analyses including high-quality exposure assessment, targeting specific subtypes and mechanisms.

## Declaration of Competing Interest

I have no competing interests.

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